PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 9/107, 7/00

A1

(11) International Publication Number: WO 96/37192

(43) International Publication Date: 28 November 1996 (28.11.96)

(21) International Application Number: PCT/IB96/00493

(22) International Filing Date: 24 May 1996 (24.05.96)

(30) Priority Data:
1561/95-0 26 May 1995 (26.05.95) CH

(71) Applicant *(for all designated States except US)*: VESIFACT AG [CH/CH]; Jöchlerweg 4, CH-6342 Baar (CH).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: WEDER, Hans, Georg [CH/CH]; Alte Landstrasse 84B, CH-8803 Rüschlikon (CH).

(74) Agent: HEPP, WENGER & RYFFEL AG; Bahnhofstrasse 58, CH-8001 Zürich (CH).

(81) Designated States: BR, CA, CN, HU, JP, KR, MX, NO, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: PHARMACEUTICAL AND COSMETIC COMPOSITIONS CONTAINING SPHINGO- AND GLYCOLIPIDS

(57) Abstract

The invention relates to pharmaceutical or cosmetic compositions for the topical, enteral or parenteral administration of sparingly soluble sphingolipids and glycolipids. The compositions are prepared by the formation of a homogeneous dispersion of nanoparticles.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia
AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

Pharmaceutical and Cosmetic Compositions containing Sphingo- and Glycolipids

The invention relates to pharmaceutical or cosmetic compositions for the topical, enteral or parenteral administration of sparingly soluble sphingolipids and glycolipids, a process for the preparation of these compositions and to the formulation base for the preparation of pharmaceutical or cosmetic compositions.

Sphingolipids are lipid molecules of complex structure which are characterized in their skeletal structure by sphingosine or bases derived therefrom. Sphingolipids contain three characteristic structural embodiments: sphingosine or base derivatives thereof, a long chain fatty acid and a hydrophilic head group, which in some sphingolipids may assume considerable bulkiness and structural complexity, e.g. gangliosides. Sphingosine is a specific representative of a group consisting of 30 different amino alcohols which are present in sphingolipids of distinct biological species. The most important bases present in sphingolipids originating from animal species, being primarily present in brain and neural tissues, are sphingosine (4-sphingenine) and dihydrosphinganine (sphinganine). The most important base present in plant varieties of higher order and yeasts is phytosphingosine (4-hydroxysphinganine). The sphingosine base or the derivative thereof is bound at the amino group by an amide bond to a long chain, saturated or unsaturated fatty acid containing about 16-30 carbon atoms. The corresponding compounds containing two non-polar long fatty acid chains are classified as ceramides. Ceramides of natural origin are charaterized by their optical activity and specific stereochemical configuration: 1S, 2S, 3R for phytosphingosine and 1S, 2S for sphingosine.

Provided that the hydroxy group in the 1-position of the sphingosine base is substituted by three different hydrophilic head groups, the corresponding compounds can be classified in the following groups:

Sphingomyelins (the polar end is phosphatidylethanolamine or phosphatidylcholine); neutral glycosphingolipids (glycosyl ceramides, galactosyl ceramides; defined by the saccharide group which is attached to the ceramide group by beta-glycoside bonds); gangliosides, also defined as

acidic gangliosides, which contain in their polar ends oligosaccharides (D-glucose, D-galactose, as well as N-acetyl-D-galactosamine groups) and which contain one or more sialic acid groups (N-acetylneuraminic acid). Gangliosides are an important embodiment of the lipid structure present in human brain.

Sphingolipids and glycolipids have antiinflammatory efficacy and influence the differentiation and proliferation of epidermal tissue. Ceramides of different structure are present in stratum corneum of human epidermis, e.g. ceramide 1, 2, 3, 4, 5, 6 I and 6 II (*D.C. Swarzendruger et al., Molecular Models, J. Invest. Derm. 92, 251 (1989)*) in a percentage of more than 40%. Also present are cholesterol, cholesterol sulfate and free fatty acids. Ceramides function primarily as an epidermal barrier of the skin, which prevents transcutaneous loss of water and protects against environmental influences.

The stratum corneum layer consists of various keratinocytes (corneocytes) and other lipids of different structure. The latter ones are arranged intracellularly in multi-bilayer structures. The "bricks and mortar" model describing the barrier to skin permeability defines the stratum corneum layer as a biphasic structure, wherein the continuous lipid phase consists of intracellular lamellae embedding corneocytes. The sphingolipids and glycolipids mentioned above are in considerable amounts part of this continous lipid phase.

The low solubility of the sphingolipids and glycolipids is a serious drawback to their therapeutic and cosmetic uses. Suitable topical (dermal) and parenteral dosage forms have hitherto not been available for these lipids. This may be explained by the fact that certain ceramides, as well as other sphingolipids and glycolipids, do not form bilayer structures similar to those known from phospholipids. It is well known that phospholipids are capable of forming bilayer structures in intracellular membranes. The formation of bilayer structures containing sphingolipids and glycolipids was only known from liposomal structures with admixed phospholipids. Liposomes as carrier systems have other drawbacks in view of their low loading capacity for sphingolipids and glycolipids.

The present invention intends to make available for therapeutic and cosmetic uses the important group of sphingolipids and glycolipids and to enable the preparation of suitable topical and parenteral dosage forms.

Numerous publications propose various means of converting a sparingly soluble therapeutic agent into a more soluble form that is suitable for intravenous formulations. Such a conversion can be carried out, for example, with the aid of so-called solubilizers, such as 1,2-propylene glycol or polyethylene glycol 300-400. In the event that solubilization is unsuccessful, a very limited group of alternative solubilizers, e.g. lecithin, still is available. But the choice among different solubilizers is extremely limited. In general, national pharmocopoeias and regulatory documents are very restrictive with respect to allowing additives having solubilizing properties for their use in parenteral and topical dosage forms.

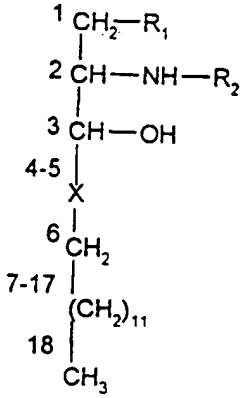
In the event that the addition of one of the few solubilizers permitted in national pharmacopoeias still fails to promote the solubility of the active agent, the incorporation in finely dispersed systems based on lipid mixtures is suggested in the prior art. In such systems, the sparingly soluble therapeutic agent is encapsulated in lipid particles of a particle size of less than 1 µm. The "loaded" lipid particles then form with the aqueous carrier liquid an aqueous phase of colloidally dispersed or, preferably, finely dispersed character, which differs from the true homogenous distribution of solutes at molecularly dispersed level but is, nevertheless, sufficiently homogenous for the preparation of intravenous and oral dosage forms. Numerous publications suggest the incorporation of therapeutic agents of low solubility in micells, mixed micells, reversed micells, unilamellar or multilamellar liposomes, nanocapsules or nanoparticles.

These methods have the definitive advantage that they are useful for converting into suitable dosage forms even therapeutic agents having a distinctly poor water solubility. However, they also have some disadvantages frequently encountered, such as inadequate stability of the dispersion due to the separation of the phase into the individual components, insufficient amounts of the therapeutic agent encapsulated, the strong dependency of the particle size on

the methods and conditions employed, unsatisfactory uniformity and insufficient reproducibility of the products obtained, and other problems. From a technical point of view the preparation of these systems appears rather complex in comparison with conventional mixing processes: there are used, for example, high-pressure homogenization, extrusion techniques, treatment with ultrasonic radiation and others and also corresponding machinery and technology. In addition, subsequent methods of separation, for example dialysis, gel filtration or sterile filtration, are generally required before such dispersions can be administered.

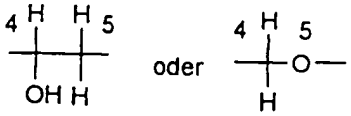
Surprisingly it has now been found that sphingolipids and glycolipids are capable of forming finely dispersed systems having the homogeneity and stability necessary for topical and parenteral dosage forms. This is achieved by dispersing sparingly soluble sphingolipids and glycolipids in combination with phospholipids and a partial fatty acid ester of polyoxyethylene sorbitan.

The present invention relates to pharmaceutical or cosmetic compositions comprising:
a) a sphingolipid or glycolipid of synthetic or natural origin of the formula:



(I),

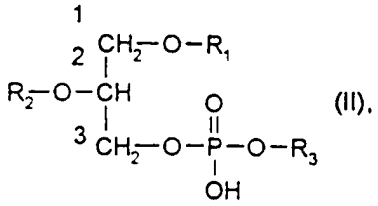
wherein X represents the ethylene or vinylen group or a bivalent group of the partial formula:



R_1 is hydroxy, the phosphatidylcholine, the phosphatidylethanolamine group or hydroxy bound as β-glycoside to a mono- or oligosaccharide group or is an oligosaccharide group substituted by N-acetylneuraminic acid groups; and

R_2 is C_{16-30}-acyl, C_{16-30}-α-hydroxyacyl or C_{16-30}-ω-hydroxyacyl, which is optionally esterified by a linoleic acid group;

b) a phospholipid of the formula



(II),

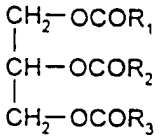
wherein R_1 is C_{10-20}acyl; R_2 is hydrogen or C_{10-20}acyl; R_3 is hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, C_{1-4}alkyl, C_{1-5}alkyl substituted by carboxy, C_{2-5}alkyl substituted by hydroxy, C_{2-5}alkyl substituted by carboxy and hydroxy, C_{2-5}-alkyl substituted by carboxy and amino, or an inositol group or a glyceryl group, or a salt of such a compound;

c) a partial fatty acid ester of polyoxyethylene sorbitan;

d) the carrier liquid water optionally admixed with C_2-C_4-alkanol in the degree of purity necessary for the intended pharmaceutical or cosmetic administration; and the following optional components:

e) a therapeutic agent to be administered;

f) a triglyceride of synthetic or natural origin of the formula



(III),

wherein R_1, R_2 und R_3 represent C_{8-20}-acyl; and

g) water-soluble or lipid-soluble additives suitable for the intended pharmaceutical or cosmetic administration.

The pharmaceutical or cosmetic compositions defined above are distinguished by useful phase properties of the solubilised therapeutic agent. For example, where opalescence and transparency occur in incident light, only an extremely slight milky turbidity reveals that the

dispersion formed still has physical differences vis-à-vis the ideal state of a true molecular solution. Electron microscope images show that a population of more than 95 % of the sparingly soluble active ingredient is present in the form of a colloid disperse system of particles having a particle size of approximately 5-20 nm (nanodispersion). However, these differences vis-à-vis a true solution are acceptable in view of some remarkable homogeneity properties of the dispersion. These properties can be made apparent in a high storage stability; for example there is no separation after storage for several months at 2-8°C (by extrapolation the expected stability is more than two years).

Within the scope of the description of the present invention, the terms used hereinbefore and hereinafter are defined as follows:

The term sphingolipid or glycolipid of synthetic origin defines lipids of the formula I, wherein segments of their molecular structure have been modified chemically, e.g. by hydration, transesterification, ester cleavage, esterification, substitution and other conventional process steps. The term synthetic lipid also defines lipids of the formula I which are obtainable by total synthesis.

The term sphingolipid or glycolipid of natural origin defines lipids of the formula I, which have only been submitted to purification processes, e.g. chromatographic separation methods, but have not been submitted to chemical modifications of their molecular structure.

Component a)

The term sphingolipid or glycolipid comprises lipids, which are defined by terms such as ceramides, sphingomyelines, cerebrosides, or gangliosides. Ceramides and sphingomyelines are classified together under the term sphingolipids, whereas cerebrosides and gangliosides are classified together under the term glycolipids.

In a ceramide of the formula I R_1 is hydroxy. Known ceramides are classified as ceramide 1, 2, 3, 4, 5, 6 I and 6 II. The group of ceramides also comprises so-called synthetic questamides,

e.g. questamide H, or so-called synthetic pseudo-ceramides, e.g. pseudo-ceramide SLE, and also lipids named ceramax. The method of preparation and the structure of natural and synthetic ceramides and derivatives thereof is known and described in the publications *Yeast Derived Ceramides (Technical Bulletin)* issued by Gist-Brocades, in the *SÖFW Journal, 121st year of publication, Volume 5/95, pages 342-348, authors H.Theis, and S.Göring,* in the *SÖFW Journal, 121st year of publication, Volume 5/95, pages 228-238, authors S.Watkins et al.* and in *Ceramides/ Cholesterol/ Free fatty acids containing cosmetics, SÖFW Journal, 122nd year of publication, Vol. 4/96, pages 199-204,* authors *K.De Paepe et al..*

The ceramides which primarily occur in human skin are defined according to INCI rules (formerly CTFA) as ceramides 3. In these ceramides 4-hydroxysphinganine (phytosphingosin) is, besides 4-sphingenine (sphingosine), the predominating sphingosine base.

In a sphingomyeline of the formula I R_1 is the the phosphatidylcholine or the phosphatidyl-ethanolamine group.

R_2 representing C_{16}-, C_{18}- and C_{24}-acyl is preferably n-hexadecanoyl (palmitoyl), n-octa-decanoyl (stearoyl), n-tetracosanoyl (lignocerinoyl), 9-cis-octadecenoyl (oleoyl) or 9-cis- or 12-cis-octadecadienoyl.

R_2 representing C_{16-30}-hydroxyacyl is preferably α-hydroxy-octadecanoyl or α-hydroxy-tetracosanoyl or a mixture thereof. Relevant to some degree are acid amides in this position formed with C_{2-10}-α-hydroxycarboxylic acids, e.g. hydroxyacetic acid (glycolic acid), 2-hydroxypropionic acid (lactic acid), 2-hydroxysuccinic acid (malic acid), α-hydroxy-phenylacetic acid (mandelic acid) or mixtures thereof.

R_2 representing C_{16-30}-ω-hydroxyacyl, preferably in the sphigosine base phytosphigosine, is, e.g. 23-octadecanoyloxytricosanoyl or 23-octadecanoyloxy-heptacosanoyl.

In a glycolipid (I) of the cerebroside type R_1 represents hydroxy bound as β-glycoside to a mono- or oligosaccharide group which is optionally substituted by N-acetyl.

Representative monosaccharide groups are D-glucosyl and D-galactosyl, as well as N-acetyl-D-glucosamine and N-acetylgalactosamine.

In a glycolipid (I) of the ganglioside-type R_1 represents hydroxy, which is also bound as β-glycoside to an oligosaccharide group containing at least three hexosyl groups, which may be substituted by at least one N-Acetylneuraminic acid groups. These lipids are classified as gangliosides. The compounds defined by the formula I are known and have been described in numerous textbooks and other references from biochemistry.

Component b)

The nomenclature used for the phospholipids (II) and the numbering of the carbon atoms (sn-nomenclature, stereospecific numbering) are in accordance with the recommendations made by the IUPAC-IUB Commission on Biochemical Nomenclature (CBN) in Eur. J. of Biochem. 79, 11-21 (1977) "Nomenclature of Lipids".

R_1 and R_2 defined as C_{10-20}acyl are preferably straight-chain C_{10-20}alkanoyl having an even number of carbon atoms and straight-chain C_{10-20}alkenoyl having from one to three double bonds and an even number of carbon atoms.

Straight-chain C_{10-20}alkanoyl R_1 and R_2 having an even number of carbon atoms are, for example, n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl or n-octadecanoyl.

Straight-chain C_{10-20}alkenoyl R_1 and R_2 having from one to three double bonds and an even number of carbon atoms are, for example, 6-cis-, 6-trans-, 9-cis- or 9-trans-dodecenoyl, -tetradecenoyl, -hexadecenoyl, -octadecenoyl or -icosenoyl, especially 9-cis-octadecenoyl (oleoyl), and also 9,12-cis-octadecadienoyl or 9,12,15-cis-octadecatrienoyl.

A phospholipid (II), wherein R_3 is 2-trimethylamino-1-ethyl, is referred to by the trivial name lecithin and a phospholipid (II), wherein R_3 is 2-amino-1-ethyl, by the trivial name cephalin. Suitable are, for example, naturally occurring cephalin or lecithin, for example cephalin or lecithin from soybeans or chicken eggs having different or identical acyl groups R_1 and R_2, or mixtures thereof.

However, the phospholipid (II) may also be of synthetic origin. The expression "synthetic phospholipid" is used to define phospholipids having a uniform composition in respect of R_1 and R_2. Such synthetic phospholipids are preferably the above-defined lecithins and cephalins, wherein the acyl groups R_1 and R_2 have a defined structure and are derived from a defined fatty acid having a degree of purity greater than approximately 95%. R_1 and R_2 may be identical or different and unsaturated or saturated. Preferably, R_1 is saturated, for example n-hexadecanoyl, and R_2 is unsaturated, for example 9-cis-octadecenoyl (= oleoyl).

The expression "naturally occurring"defines a phospholipid (II) that does not have a uniform composition in respect of R_1 and R_2. Such natural phospholipids are likewise lecithins and cephalins, wherein the acyl groups R_1 and R_2 are structurally undefinable and are derived from naturally occurring fatty acid mixtures.

The requirement "substantially pure" defines a phospholipid (II) having a degree of purity of more than 90 % (by weight), preferably more than 95 %, which can be demonstrated by means of suitable determination methods, for example by paper chromatography, by thin-layer chromatography, by HPLC or by means of enzymatic colour testing.

In a phospholipid (II), R_3 defined as C_{1-4}alkyl is, for example, methyl or ethyl. Methyl is preferred.

R_3 defined as C_{1-5}alkyl substituted by carboxy, C_{2-5}alkyl substituted by hydroxy or C_{2-5}alkyl substituted by carboxy or hydroxy is, for example, 2-hydroxyethyl, 2,3-dihydroxy-n-propyl,

carboxymethyl, 1- or 2-carboxyethyl, dicarboxymethyl, 2-carboxy-2-hydroxyethyl or 3-carboxy-2,3-dihydroxy-n-propyl.

R_3 defined as C_{2-5}alkyl substituted by carboxy and amino is, for example, 3-amino-3-carboxy-n-propyl or 2-amino-2-carboxy-n-propyl, preferably 2-amino-2-carboxyethyl. A phospholipid (I) having those groups may be in salt form, for example in sodium or potassium salt form.

Phospholipids (II) wherein R_3 is the inositol or the glyceryl group are known by the names phosphatidylinositol and phosphatidylglycerol.

The acyl radicals in the phospholipids (II) and in the other components are also customarily known by the names given in brackets:

9-cis-Dodecenoyl (lauroleoyl), 9-cis-tetradecenoyl (myristoleoyl), 9-cis-hexadecenoyl (palmitoleoyl), 6-cis-octadecenoyl (petroseloyl), 6-trans-octadecenoyl (petroselaidoyl), 9-cis-octadecenoyl (oleoyl), 9-trans-octadecenoyl (elaidoyl), 11-cis-octadecenoyl (vaccenoyl), 9-cis-icosenoyl (gadoleoyl), n-dodecanoyl (lauroyl), n-tetradecanoyl (myristoyl), n-hexadecanoyl (palmitoyl), n-octadecanoyl (stearoyl), n-icosanoyl (arachidoyl), n-docosanoyl (behenoyl), n-tetracosanoyl (lignoceroyl).

A salt of the phospholipid (II) is pharmaceutically acceptable. Salts are defined by the existence of salt-forming groups in the substituent R_3 and by the free hydroxy group at the phosphorus atom. The formation of internal salts is also possible. Alkali metal salts, especially the sodium salt, are preferred.

In an especially preferred embodiment of this invention, purified lecithin from soybeans, for example of the LIPOID S 100 or S 100-35 types (partially hydrated lecithin), is used.

Component c)

The above-mentioned partial fatty acid ester of polyoxyethylene sorbitan consists preferably of a substantially pure ester of sorbitan or a mixture of different esters of sorbitan in which the structure of the fatty acid groups and the length of the polyoxyethylene chains may vary. The hydrophilic sorbitan is preferably etherified by three hydrophilic polyoxyethylene chains and esterified by a hydrophobic fatty acid group. The sorbitan may, however, alternatively be etherified by only one or two polyoxyethylene chains and correspondingly esterified by two or three fatty acid groups. The basic sorbitan structure is altogether substituted by a minimum of two and a maximum of three hydrophilic groups, the term "hydrophilic group" embracing the polyoxyethylene chains, whereas the fatty acid groups are hydrophobic.

The polyoxyethylene chain is linear and has preferably from 4 to 10, especially from 4 to 8, ethylene oxide units. The ester groups on the basic sorbitan structure are derived from a saturated or unsaturated, straight-chain carboxylic acid having an even number of from 8 to 20 carbon atoms. The ester group derived from that carboxylic acid is preferably straight-chained having 12, 14, 16 or 18 carbon atoms, for example n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl or n-octadecanoyl. The ester group derived from an unsaturated carboxylic acid having an even number of from 8 to 20 carbon atoms is preferably straight-chained having 12, 14, 16 or 18 carbon atoms, for example oleoyl. The mentioned esters of sorbitan are in conformity with the data given in the British Pharmacopoeia (specialised monograph) or Ph.Helv.VII. In particular, the product specifications published by the mentioned manufacturers with the information on data sheets for the relevant product, especially specifications such as shape, colour, HLB value, viscosity, ascending melting point and solubility, apply.

Suitable partial fatty acid esters of polyoxyethylene sorbitan are commercially obtainable under the trademark Tween® of ICI Corp. and known by the chemical names polyoxyethylene-(20 or 4)sorbitan monolaurate (TWEEN 20 and 21), polyoxyethylene(20)sorbitan monopalmitate or monostearate (TWEEN 40 and 60), polyoxyethylene(4 or 20)sorbitan monostearate or tristearate (TWEEN 61 and 65), polyoxyethylene(20 or 5)sorbitan monooleate

(TWEEN 80 or 81) and polyoxyethylene(20)sorbitan trioleate (TWEEN 85). In an especially preferred embodiment of the invention, polyoxyethylene(20)sorbitan monooleate (TWEEN 80) is used as component c).

Component d)

The carrier liquid water is optionally admixed with a C_2-C_4-alkanol, especially ethanol, and is present in the composition in the degree of purity necessary for the intended pharmaceutical or cosmetic administration. In the event that parenteral administration is intended, water has the degree of purity prescribed for injection formulations in accordance with the regulations of the national pharmacopoeias, such as the U.S. Pharmacopoeia (USP) or the Deutsches Arzneibuch (DAB) and is germ- and pyrogenfree. Water is germfree when topical dosage forms or cosmetic uses are intended. The carrier liquid ethanol is optionally admixed as C_2-C_4-alkanol when parenteral dosage forms are intended. In that event ethanol is present, ethanol has the degree of purity (at least 96 %) prescribed for injection formulations. The proportion of ethanol for injection formulations may vary within wide limits from about 1 % to about 10 %. For topical dosage forms or cosmetic uses, ethanol, isopropanol or mixtures thereof may be optionally admixed as C_2-C_4-alkanol. The proportion of C_2-C_4-alkanol for topical formulations or cosmetic uses may vary within wide limits from about 0,1% to about 10 %, preferably 0.1 % to 2.0 %.

Component e)

A therapeutic agent to be administered is any therapeutic agent or a combination of different therapeutic agents which is suitable for intended mode of administration, e.g. topical, parenteral, e.g. intramuscular in the form of injection dispersions, or oral, e.g. in the form of capsule fillings. A preferred therapeutic agent is sparingly soluble in water and has a solubility in water of less than 500 mg/1000 ml, especially of less than 100 mg/1000 ml.

Particularly suitable are corticoids for dermal administration, e.g. halogenated corticoids, e.g. amcinonide, dexamethasone, triamcinolone-16α,27α-acetonide, betamethasone (17-valerate), flumetasone (21-pivalate), flupredniden-21-acetate, clobetasol-17-propionate, mometasone-17-

(2-furoate), diflorasone-17,21-diacetate, fluocinolone acetonide, clocortolone-21-pivalate or 21-hexanoate, diflucortolone-21-valerate, fludroxycortide, halometasone, fluocinonide, or fluocortinbutyl; or non-halogenated corticoids, e.g. prednisolone, methyl prednisolone aceponate, or hydrocortisone or derivatives thereof, e.g. hydrocortisone-17-butyrate or acetate.

These corticoids may also be combined with antimycotic, sulfonamides or estrogen derivatives. Suitable for dermal formulations are also adstringents, anti-acne agents, antipsoriasis agents, or antipruriginosis agents.

Particularly suitable for topical administration are also dermal antibiotics, e.g. tetracyclin, erythromycin, fusidinic acid, framycetine sulfate, neomycin, meclocyclin, gentamycin, leucomycin, streptomycin, ganefromycin, rifamexil, ramoplanin, spiramycin, clindamycin, bacitracin, oxytetracyclin, sulfonamides, and other antibacterial and antiviral agents, e.g. podophyllotoxin, idoxuridin, heparine, foscarnet, vidarabine, tromantadine, idoxuridine, aciclovir, antimycotic agents, e.g. nystatin, amphotericin, flucytosine, miconazole, fluconazole, griseofulvine, terbinafine, natamycin, clotrimazole, econazole, fenticonazole, omoconazole, bifonazole, oxiconazole, tioconazole, ketoconazole, ciclopiroxalamine, naftifine, terbinafine, amorolfine, tolnaftate, or ciclopirox and the corresponding salts thereof. The above-mentioned antibiotics and antimycotic agents may be combined with other corticosteroids, antibiotics or antimycotic agents.

Particularly suitable for topical administration are also lipophilic vitamins, typically vitamin A (retinol, free acid or derivatives thereof), B (B_1: thiamine, B_2: riboflavine, B_6: pyridoxin, panthenol, pantothenic acid , vitamin B_{12} and combinations thereof), vitamin C, D, E (tocopherol), biotin or vitamin K; also retinoids and carotinoids.

Suitable for topical, parenteral, eg. intramuscular, or oral administration, e.g. as capsule fillings are sparingly soluble therapeutic agents, e.g. immunosuppressants having a macrolide structure, typically cyclosporin A, cyclosporin G, rapamycin, tacrolimus, deoxyspergualin, mycophenolate-mofetil, gusperimus, non-steroidal antiphlogistic agents and salts thereof,

typically acetylsalicylic acid, ibuprofen or S(+)-ibuprofen, indomethacin, diclofenac (Na and K-salt), piroxicam, meloxicam, tenoxicam, naproxen, ketoprofen, flurbiprofen, fenoprofen, felbinac, sulindac, etodolac, oxyphenbutazone, phenylbutazone, nabumetone; dihydropyridine derivatives having cardiovascular activity, e.g. nifedipine, nitrendipine, nimodipine, nisoldipine, isradipine, felodipine, amlodipine, nilvadipine, lacidipine, benidipine, masnipine, furnidipine, niguldipine; immunodepressants and stimulants, typically a-liponic acid, muramyl peptides, e.g. muramyl dipeptide or muramyl tripeptide, romurtid, alkaloids, e.g. vincopectin, vincristine, vinblastin, reserpine, codeine, ergot alkaloids, typically bromocriptine, dihydroergotamine, dihydroergocristine; antitumour agents, e.g. chlorambucil, etoposide, teniposide, idoxifen, tallimustin, teloxantron, tirapazamine, carzelesin, dexniguldipine, intoplicin, idarubicin, miltefosin, trofosfamide, teloxantrone, melphalan, lomustine, 4,5-bis(4'fluoroanilino)-phthalimide; 4,5-dianilinophthalimide; immunomodulators, typically thymoctonan, prezatid copper acetate; H2-receptor antagonists, typically famotidine, cimetidine, ranitidine, roxatidine, nizatidine, omeprazole, proteinkinase inhibitors; or HIV-1protease inhibitors or leucotriene antagonists.

Instead of being in the form of a free acid or in basic form, the above-mentioned therapeutic agent may be present in the pharmaceutical composition in the form of a pharmaceutically acceptable salt, typically as hydrobromide, hydrochloride, mesylate, acetate, succinate, lactate, tartrate, fumarate, sulfate, maleate, and the like.

The concentration of the therapeutic agent or combination thereof is determined by the dosage to be administered and can be in the range from 1.0 to 30.0 % by weight, preferably from 5.0 to 20.0 % by weight, more particularly from 5.0 to 12.0 % by weight, based on the weight of the carrier composition.

Component f)

In a triglyceride of the formula III used as component f), R_1, R_2 and R_3 are straight-chain C_8-C_{24}-acyl having an even number of carbon atoms, especially n-octanoyl, n-dodecanoyl, n-tetra-decanoyl, n-hexadecanoyl, n-octadecanoyl, 9-cis-dodecenoyl, 9-cis-tetradecenoyl, 9-cis-hexa-

decenoyl, 9-cis-octadecenoyl or 9-cis-icosenoyl. The definitions of R_1, R_2 and R_3 may be identical or different, whereas the individual groups R_1, R_2 and R_3 themselves are being defined by their uniform structure, which is characteristic of synthetic or semi-synthetic triglycerides. R_1, R_2 and R_3 may, however, alternatively consist of various acyl groups of different structures, which is characteristic of triglycerides of natural origin.

A triglyceride of formula III is a semi-synthetic or synthetic, substantially pure triglyceride or a pharmaceutically acceptable triglyceride of natural origin. A triglyceride of natural origin is preferred, for example groundnut, sesame, sunflower, olive, maize kernel, soybean, castor, cottonseed, rape, thistle, grapeseed, fish or coconut oil. In an especially preferred embodiment of the invention, a triglyceride having different acyl groups of different structure defined by the term "neutral oil" is used, for example a triglyceride of fractionated coconut C_8-C_{10} fatty acids of the Miglyol® type, e.g. MIGLYOL 812.

The optional component cholesterol is preferably purified cholesterol from lanolin (5-cholest-en-3ß-ol) and has a degree of purity of 96-97% in accordance with the regulations of *The U.S. Pharmacopoeia National Formulary (USP/NF).*

Component g)

Typical additives may be present in the composition which are characteristic for the intended pharmaceutical dosage form or cosmetic uses. They have the degree of purity in accordance with the regulations of the national pharmacopoeias mentioned above. Depending on the intended use, additives may be water soluble or lipid soluble. Suitable additives are useful for the preparation of o/w, w/o, w/o/w emulsions, gels, ointments, creams, oils, lotions, foams, or sprays. The addition of preserving agents, antioxidants, stabilizers or softening agents is recommended. A preferred additive in topical pharmaceutical and cosmetic compositions is cholesterol or a corresponding salt thereof, e.g. cholesterol sulfate in the degree of purity necessary for the intended cosmetic or pharmaceutical administration.

Suitable additives for pharmaceutical and particularly cosmetic compositions are also free fatty acids derived by conventional ester cleavage from the above-mentioned triglycerides (III), surfactants, e.g. anionic, cationic, or amphoteric, gel-forming agents, emulsifiers, e.g. ethoxylated fatty alcohols, hydrogenated ethoxylated castor oils, partial esters of fatty acids and modified fatty acids with glycerol, polycerol, and sorbitol, orthophosphoric acid esters, or silicone surfactants, lipophilic constituents, e.g. solid, semisolid, and liquid hydrocarbons, natural oils and waxes, silicone oil, guerbet alcohols, fatty acid esters, isostearic acid derivatives, co-emulsifiers, thickeners, gelling agents, foam stabilizers, fat-restoring substances, pearl-luster and turbidity agents, preservatives, dyes, colored pigments, perfume oils, and preferably light filters (sunscreens).

Preferred as sunscreens are active agents such as UV-B filtering substances, e.g. 4-amino-benzoic acid, homosalate, oxybenzon, 3-imidazolyl-4-yl-acrylic acid and derivatives thereof, 2-phenylbenzimidazol-5-sulfonic acid and salts thereof; 2,3-dihydroxypropyl-4-amino-benzoate, 2-ethylhexyl-4-dimethyl-aminobenzoate, ethyl 4-[bis(2-hydroxypropyl)amino]benzoate, 2-ethylhexyl-4-methoxy-cinnamate, 2-ethylhexylsalicylate, ethylpoly(oxyethylene)-4-{bis-[(2-hydroxyethyl)-polyoxyethylene]amino}benzoate, 3-(4-imidazolyl)acrylic acid, isopentyl 4-methoxycinnamate, 4-isopropylbenzyl salicylate, α-(2-oxo-3-bornylidene)-toluene, α-(2-oxo-3-bornylidene)-toluene sulfonic acid, α-(2-oxo-3-bornylidene)-toluene-p-xylene, 2-phenyl-5-benzimidazole sulfonic acid, 3,3,5-trimethylcyclohexylsalicylate, N,N,N-trimethyl-α-(2-oxo-3-bornylidene)-toluene-p-toluidiniummethylsulfate, or octyl triazone, or UV-A filtering substances, e.g. butyl methoxydibenzoylmethane, isopropyldibenzoylmethane, benzophenone-4, 3, or 10 or Colipa S 71. Suitable sunscreens are listed in *Pflegekosmetik: Ein Leitfaden, W.Raab, U.Kindl; Govi-Verlage, D-Frankfurt 1991* and in *Ullmann's Encyclopedia of Industrial Chemistry, VCH Publishers, Fifth Complete Revised Edition, Volume A 24, Entry Skin Cosmetics.*

The following embodiments of the invention are particularly preferred; the designation by letters of the above-mentioned components is adhered to:

A pharmaceutical or cosmetic composition comprising:

a) a natural or synthetic ceramide or a derivative or mixtures thereof;

b) purified lecithin from soy beans;

c) at least one partial fatty acid ester of polyoxyethylene sorbitan;

d) ethanol and water as carrier liquids;

f) a triglyceride selected from the group of natural triglycerides; and as optional components:

e) a therapeutic agent to be administered;

g) cholesterol or a corresponding salt thereof; and other water-soluble or lipid-soluble additives suitable for the intended pharmaceutical or cosmetic administration.

A pharmaceutical or cosmetic composition comprising:

a) a synthetic ceramide or a derivative thereof;

b) purified lecithin from soy beans;

c) polyoxyethylene(20)sorbitan monooleate;

d) ethanol and water as carrier liquids;

f) a triglyceride selected from the group of natural triglycerides; and as optional components:

e) a therapeutic agent to be administered;

g) cholesterol or a corresponding salt thereof; and other water-soluble or lipid-soluble additives suitable for the intended pharmaceutical or cosmetic administration.

A pharmaceutical or cosmetic composition comprising:

a) N-(9-cis-Octadecenoyl)-phytosphingosine (Ceramide 3B);

b) purified lecithin from soy beans;

c) polyoxyethylene(20)sorbitan monooleate;

d) ethanol and water as carrier liquids;

f) a triglyceride selected from the group of natural triglycerides; and as optional components:

e) a therapeutic agent to be administered;

g) cholesterol or a corresponding salt thereof; and other water-soluble or lipid-soluble additives suitable for the intended pharmaceutical or cosmetic administration.

The invention relates also to the process known *per se* for the preparation of the pharmaceutical or cosmetic composition, which process comprises preparing an aqueous dispersion by homogeneously mixing components a), b), c) and d) and the optional components e), f) and g) and subjecting the dispersion obtainable to the following subsequent operations:

α) addition of a further amount of water as carrier liquid and optionally further water-soluble excipients that are suitable for the intended pharmaceutical dosage forms or cosmetic compositions; filtration and optionally dialysis of the clear dispersion; or

β) filtration and optionally dialysis and subsequent conversion of the dispersion obtainable into a dry preparation, optionally with the addition of water-soluble excipients, and reconstitution of the dry preparation to form an injectable dispersion; or

γ) further processing the dispersion obtained containing nanoparticles of the sparingly soluble sphingolipids and glycolipids (nanodispersion) to the intended pharmaceutical dosage forms or cosmetic compositions.

In a preferred embodiment of the invention a pharmaceutical composition suitable for topical or dermal administration containing nanorparticles of the sparingly soluble sphingolipids and glycolipids is prepared.

In another preferred embodiment of the invention a cosmetic composition containing ceramides and optionally sunscreens is prepared.

In another preferred embodiment of the invention, a formulation base is prepared as follows: To the phospholipid (II), component b, the carrier liquid ethanol, component d) then is added. To this dispersion, cholesterol, component g), the sparingly soluble sphingolipids and glycolipids (I), component a), a partial fatty acid ester of polyoxyethylene sorbitan, component c). a triglycerid (III), component f) and further lipophilic additives, component g), are added, which are suitable for the intended pharmaceutical dosage forms or cosmetic compositions.

The clear ethanolic dispersion containing the sparingly soluble sphingolipids and glycolipids (I), which may simply be defined as preparticular ceramide dispersion, is stable under normal

storage conditions (room temperature, light protection) up to one year and more. The dispersion containing nanoparticles of the sparingly soluble sphingolipids and glycolipids (I) is prepared by adding the formulation base consisting of the preparticular ceramide dispersion to the carrier liquid water. Further water-soluble additives, component g), are added, which are suitable for the intended pharmaceutical dosage forms or cosmetic compositions.

The invention also relates to the pharmaceuticla formulation base (preparticular ceramide dispersion) containing the components a), b), c), ethanol, and the optional components f) and g).

The invention also relates to an active agent free pharmaceutical formulation base containing the components a), b), c) and the carrier liquids ethanol and water, component d), and the optional components f) and g). This formulation base is useful as placebo formulation or as precursor of the above-mentioned pharmaceutical composition to which a suitable active agent e) is added.

The invention also relates to a pharmaceutical composition, wherein the solubilisation of a sparingly soluble active ingredient is required, e.g. capsule fillings, drops, lotions, or emulsions form ointments, gels, creams etc..Other excipients typical of such dosage forms may be added.

The invention also relates to a cosmetic composition containing the components a), b), c) and d), and the optional components f) and g), which is particularly suitable for the preparation of cosmetic sunscreen compositions.

The preparation of the formulation base and, in the alternative, of the cosmetic composition, is performed in a manner analogous to the methods described above. A process temperature of about 20° to room temperature is particularly preferred. A process temperature of about 35-45°C is preferred when cholesterol is added to the composition.

When preparing the dispersion, mixing can be effected by vigorous shaking using a dispersing machine, for example a Vortex mixer, or using dispersing machines of the POLYTRON type (Kinematica AG, Littau Switzerland) or dispersing machines produced by IKA (Staufen, Germany), a static mixer and conventional stirring machines having a propeller or paddle blade or using a magnetic stirrer or phase mixer. In order to obtain an especially homogeneous mixture, stirring is carried out at moderate or high speed, for example using stirring machines produced by Polytron, for example Polytron PT 3000 or DH 30/30. Approximately from 0.1 to 50 % by weight of the constituents (without the water component), based on the total weight of the dispersion, preferably approximately from 2 to 33 % by weight, can be dispersed in the aqueous phase. Since phospholipids are used (component b)), observation of the so-called phase transition temperature (gel-form/liquid crystalline) of the phospholipids used is critical. Dispersion is preferably effected at temperatures at which the phospholipid used is present in the liquid-crystalline state, that is to say above the so-called phase transition temperature. A phospholipid that is in the liquid crystalline state at room temperature or lower temperatures, for example lecithin from soybeans, is especially suitable.

The mixture obtainable can be defined as a dispersion of colloidal nanoparticles of the sparingly soluble sphingolipids and glycolipids, or, more simply, as a nanodispersion. By means of measurements from laser light scattering and electron micrographs, the colloidal particles present in the dispersion can be distinguished from other particles such as liquid crystals, micelles, inverse micelles or liposomes. For the statistical plurality of more than 90 %, especially more than 95 %, an average particle size of less than 30-50 nm is typical.

For the identification of the nanodispersion obtainable, methods known *per se* are suitable, for example optical examination: a slight to intense opalescence of the preparation is easily identifiable (indicates average particle size of less than 50 nm); laser light scattering (determination of the particle size and homogeneity); or electron microscopy (freeze fracture and negative contrast technique).

Subsequent operations

The necessary amount of water, which must be of the purity prescribed for injectables, can be added to the nanodispersion. This nanodispersion can be directly administered after selecting the filtration method suitable for such types of dispersions, for example sterile gel filtration, for example using Sepharose® or Sephacryl® (Pharmacia) as carrier, or preferably sterile filtration (0.2 mm), for example with a PAL filter (Gelman), and optionally after adding further water-soluble excipients that can be used for intravenous dosage forms. Especially sterile-filtration is applicable to separate off all the relatively large particles in the dispersion having a diameter greater than about 200 nm, as well as floating and solid substances, and excess, dispersed lipids which may be present in high-molecular-weight aggregates. This yields a nanodispersion having a high proportion of hydrophilic particles of relatively uniform size. Alternatively or in addition to sterile filtration, the nanodispersion can be subjected to dialysis and/or ultrafiltration for the purpose of purification.

As an alternative to the preparation of a directly administrable nanodispersion, the subsequent purification steps described above may be carried out and the purified nanodispersion may be converted into a dry preparation, especially into a lyophilisate, which is reconstituted prior to administration by the addition of water. An administrable nanodispersion is obtained again after reconstitution of the lyophilisate. For the preparation of lyophilisates, the addition of so-called builders, such as lactose or mannitol, is customary. These excipients are added in such amounts that after reconstitution of the lyophilisate the nanodispersion to be administered has isotonic properties.

Measured amounts of nanodispersion are introduced, optionally in the form of a concentrate, into containers suitable for a unit dose, for example glass ampoules (vials). The filled containers can be cooled, if desired, to about -40° to -50°C, especially to about -45°C, and then lyophilised at a pressure of about 0.2 to 0.6 mbar by slowly heating to a final temperature of about 25° to 35°C.

The sphingolipid- or glycolipid-containing compositions of the present invention are particularly suitable for topical application on skin and hair. Ceramides, for instance, are highly effective in maintaining, improving, restoring and protecting the water impermeabilty barrier of the skin. In particular, ceramides have a high capacity for recovering diminished water-retaining properties of the skin. In addition, pretreatment of the skin with the sphingolipid (ceramide) containing compositions of the invention shows a clear protecting effect against skin damage caused by external challenges. Also, on healthy skin the compsitions produce a clear moisturizing effect.

All these effects can be assessed, among others, by Corneometry (skin-hydration), Profilometry (anti-wrinkle, smoothness), TEWL (trans epidermal waterloss) and Chromametry (skin-redness) and visual inspection.

The following examples illustrate the invention and the general operability thereof. Temperatures are given in degrees Celsius.

Example 1: Formulation for 1000 g ethanolic formulation base containing ceramide 3B in a concentration of 1.5 %.

15.0 g	N-(9-cis-Octadecenoyl)-phytosphingosine (Ceramide 3B)
170.0 g	LIPOID S 100
140.0 g	Ethanol (abs.)
335.0 g	TWEEN 80 (Ph. Eur. II)
340.0 g	MIGLYOL 812
1000.0 g	Batch

To LIPOID S 100 ethanol is given. The dispersion is stirred for 30 min. at room temperature with a magnetic stirrer at about 500-1000 rpm. Ceramide 3 B is added. The dispersion is stirred again under the same conditions. TWEEN 80 is added and MIGLYOL 812. Stirring

under the same conditions. The process steps are carried out under sterile conditions and the dispersion is stored at room temperature and protected against light.

Example 2: Formulation for 100 spray formulations for the dermal application à 30 ml and 45 mg Ceramide 3B.

4.5 g	N-(9-cis-Octadecenoyl)-phytosphingosine (Ceramide 3B)
51.0 g	LIPOID S 100
42.0 g	Ethanol (abs.)
100.5 g	TWEEN 80 (Ph. Eur. II)
102.0 g	MIGLYOL 812
15.0 g	Phenoxyethanol
2685.0 g	Aqua Purificata
3000.0 g	Batch

The aqueous phase wherein the preparticular ceramide dispersion according to Example 1 is dispersed, is prepared dissolving phenoxyethanol in water at room temperature. The spray formulation is prepared from nine parts of the aqueous solution and one part of the preparticular ceramide dispersion according to Example 1. This dispersion is heated up to 45°. The aqueous solution is also heated up to 45°. The preparticular ceramide dispersion is then added to the aqueous solution. The dispersion is stirred for 30 min. at 45° with a magnetic stirrer at about 1000 rpm. The nanodispersion is sterile-filtered (pore filter 0.2 μ) and introduced into containers under sterile conditions. The nanodispersion is stored at 4° to room temperature and protected against light. The size of the nanoparticles obtained is 10-15 nm as determined by Laserlight scattering methods.

Example 3: Formulation for 100 dispensing units (nanosuspension lotion for dermal administration) à 30 ml and 60 mg Ceramide 3B.

6.0 g	N-(9-cis-Octadecenoyl)-phytosphingosine (Ceramide 3B)
68.0 g	LIPOID S 100
56.0 g	Ethanol (abs.)
134.0 g	TWEEN 80 (Ph. Eur. II)
136.0 g	MIGLYOL 812
15.0 g	Phenoxyethanol
6.0 g	GERMAL II
4.5 g	CARBOPOL 1342
120.0 g	Silbione Huile 70047/V350 (Silicon oil)
12.0 g	10 % aqueous sodium hydroxide solution
2442.5 g	Aqua Purificata
3000.0 g	Batch

The process steps are carried out in a manner analogous to Examples 1 and 2. The components are dispersed at room temperature and under mild vacuum conditions. Phenoxyethanol and GERMAL II are dissolved in water. CARBOPOL is then added carefully under stirring. The mixture is stirred at 1500 rpm for about 15 min.. The silicone oil is then added under stirring. The preparticular ceramide dispersion is then added to the aqueous solution. The dispersion is stirred for 15 min. at room temperature at about 1500 rpm. The sodium hydroxide solution is added. The dispersion is again stirred for 15 min. at room temperature at about 1500 rpm. The size of the nanoparticles obtained is 10-15 nm as determined by Laserlight scattering methods.

Example 4: Formulation for 20 injection formulations à 5ml and 25 mg ceramide 3 B

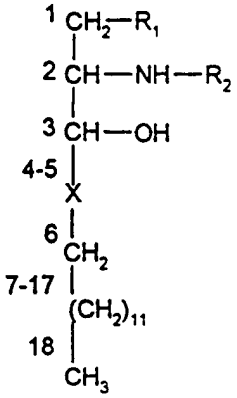
0.5 g	N-(9-cis-Octadecenoyl)-phytosphingosine (Ceramide 3B)
2.4 g	LIPOID S 100-35 (partially hydrated lecithin from soy beans)
3.2 g	Ethanol (abs.)
0.1 g	Cholesterol (purum NF)
2.2 g	TWEEN 80 (Ph. Eur. II)
0.6 g	MIGLYOL 812
91.0 g	Sodium chloride solution (0.9%)
100.0 g	Batch

LIPOID S 100-35 is dissolved in ethanol and stirred with a magnetic stirrer at about 40°. Cholesterol is then added and the mixture is again stirred at about 40°. Ceramide 3 B is given to the mixture, which is stirred for about 15 min. at about 40°. This batch is then mixed, in sequential order, with TWEEN 80 and MIGLYOL 812 and stirred for about 10 min. at 40° until the mixtures becomes clear. The sodium chloride solution is heated to 40° and added under stirring to the reaction mixture. The nanodispersion is then sterile-filtered (pore filter 0.2 µm) and introduced into containers under sterile conditions. The nanodispersion is stored at room temperature and protected against light.

Claims

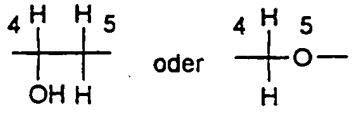
1. A pharmaceutical or cosmetic composition comprising:

a) a sphingolipid or glycolipid of synthetic or natural origin of the formula:



(I),

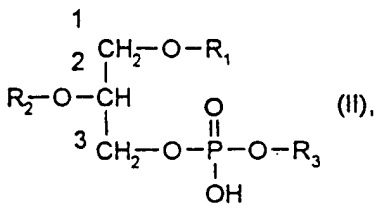
wherein X represents the ethylene or vinylen group or a bivalent group of the partial formula:



R_1 is hydroxy, the phosphatidylcholine, the phosphatidylethanolamine group or hydroxy bound as β-glucoside to a mono- or oligosaccharide group or is an oligosaccharide group substituted by N-acetylneuraminic acid groups; and

R_2 is C_{16-30}-acyl, C_{16-30}-α-hydroxyacyl or C_{16-30}-ω-hydroxyacyl, which is optionally esterified by a linoleic acid group;

b) a phospholipid of the formula



(II),

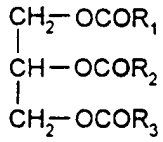
wherein R_1 is C_{10-20}acyl; R_2 is hydrogen or C_{10-20}acyl; R_3 is hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, C_{1-4}alkyl, C_{1-5}alkyl substituted by carboxy, C_{2-5}alkyl substituted by hydroxy, C_{2-5}alkyl substituted by carboxy and hydroxy, C_{2-5}alkyl substituted by carboxy and amino, or an inositol group or a glyceryl group, or a salt of such a compound; and/or

c) a partial fatty acid ester of polyoxyethylene sorbitan;

d) the carrier liquid water optionally admixed with C_2-C_4-alkanol in the degree of purity necessary for the intended pharmaceutical or cosmetic administration; and the following optional components:

e) a therapeutic agent to be administered;

f) a triglyceride of synthetic or natural origin of the formula



(III),

wherein R_1, R_2 und R_3 represent C_{8-20}-acyl; and

g) water-soluble or lipid-soluble additives suitable for the intended pharmaceutical or cosmetic administration.

2. A pharmaceutical composition according to claim 1, which contains corticosteroids as active agents.

3. A cosmetic composition according to claim 1, which contains UV-absorbers (sun screens) as active agents

4. A cosmetic compostion according to claim 1 comprising:

a) a natural or synthetic ceramide or a derivative or mixtures thereof;

b) purified lecithin from soy beans;

c) at least one partial fatty acid ester of polyoxyethylene sorbitan;

d) ethanol and water as carrier liquids;

f) a triglyceride selected from the group of natural triglycerides; and as optional components:

e) a therapeutic agent to be administered;

g) cholesterol or a corresponding salt thereof; and other water-soluble or lipid-soluble additives suitable for the intended pharmaceutical or cosmetic administration.

5. A pharmaceutical or cosmetic composition according to claim 1 comprising:

a) a synthetic ceramide or a derivative thereof;

b) purified lecithin from soy beans;

c) polyoxyethylene(20)sorbitan monooleate;

d) ethanol and water as carrier liquids;

f) a triglyceride selected from the group of natural triglycerides; and as optional components:

e) a therapeutic agent to be administered;

g) cholesterol or a corresponding salt thereof; and other water-soluble or lipid-soluble additives suitable for the intended pharmaceutical or cosmetic administration.

6. A pharmaceutical or cosmetic composition according to claim 1 comprising:

a) N-(9-cis-Octadecenoyl)-phytosphingosine (Ceramide 3B)

b) purified lecithin from soy beans;

c) polyoxyethylene(20)sorbitan monooleate;

d) ethanol and water as carrier liquids;

f) a triglyceride selected from the group of natural triglycerides; and as optional components:

e) a therapeutic agent to be administered;

g) cholesterol or a corresponding salt thereof; and other water-soluble or lipid-soluble additives suitable for the intended pharmaceutical or cosmetic administration.

7. Formulation base containing the components a), b), c) defined in any one of claims1, 4, 5 or 6, ethanol and the optional components f) and g) defined in any one of claims1, 4, 5 or 6.

8. Formulation base containing the components a), b), c) defined in any one of claims1, 4, 5 or 6, the carrier liquids ethanol and water, component d), and the optional components f) and g) defined in any one of claims1, 4, 5 or 6.

9. Formulation base according to claim 7, which contains the component e) defined in any one of claims1, 4, 5 or 6.

10. Formulation base according to claim 8, which contains the component e) defined in any one of claims1, 4, 5 or 6.

11. Process for the preparation of the pharmaceutical or cosmetic composition according to claim 1, which process comprises preparing an aqueous dispersion by homogeneously mixing components a), b), c) and d) and the optional components e), f) and g) and subjecting the dispersion obtainable to the following subsequent operations:

α) addition of a further amount of water as carrier liquid and optionally further water-soluble excipients that are suitable for the intended pharmaceutical dosage forms or cosmetic compositions; filtration and optionally dialysis of the clear dispersion; or

β) filtration and optionally dialysis and subsequent conversion of the dispersion obtainable into a dry preparation, optionally with the addition of water-soluble excipients, and reconstitution of the dry preparation to form an injectable dispersion; or

γ) further processing the dispersion obtained containing nanoparticles of the sparingly soluble sphingolipids and glycolipids (nanodispersion) to the intended pharmaceutical dosage forms or cosmetic compositions.

12. The nanodispersion obtainable by the process according to claim 11.

13. Use of the pharmaceutical and/or cosmetic composition according to claims 1-6 for maintaining, improving, restoring and protecting the water impermeability barrier of the skin.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 96/00493

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/107 A61K7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	EP,A,0 711 557 (CIBA GEIGY AG ;VESIFACT AG (CH)) 15 May 1996 see claims 1-5	1-13
X Y	EP,A,0 500 437 (OREAL) 26 August 1992 see claims 8,11; examples 3,5	1-3 7-13
Y	FR,A,2 614 787 (POLA KASEI KOGYO KK) 10 November 1988 see claims 1,5,7; example 1	1-13
Y	EP,A,0 406 162 (WEDER HANS G) 2 January 1991 see the whole document	1-13
Y	EP,A,0 257 454 (MORISHITA PHARMA) 2 March 1988 see the whole document	1-13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
18 July 1996	09. 08. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Foerster, W

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 96/00493

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 15736 (PHARMOS CORP) 19 August 1993 see the whole document	1-13
Y	US,A,5 368 857 (CORCORAN CATHLEEN ET AL) 29 November 1994 see claims 1-3; example 1	1-13
Y	WO,A,94 10131 (QUEST INT ;UNILEVER PLC (GB); UNILEVER NV (NL)) 11 May 1994 see examples 5,8	1-13
A	WO,A,93 20038 (GIST BROCADES NV ;SMEETS JAN WILLEM HUBERT (NL); WEBER PIETER GIJS) 14 October 1993 see the whole document	1-13
A	WO,A,94 23694 (UNILEVER PLC ;UNILEVER NV (NL)) 27 October 1994 see examples 1-4	1-13

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 96/00493

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0711557	15-05-96	AU-B-	3661695	23-05-96
		AU-B-	3661795	23-05-96
		CA-A-	2162341	10-05-96
		CA-A-	2162342	10-05-96
		EP-A-	0711556	15-05-96
		NO-A-	954485	10-05-96
		NO-A-	954486	10-05-96
EP-A-0500437	26-08-92	FR-A-	2673179	28-08-92
		AT-T-	125529	15-08-95
		CA-A-	2061692	22-08-92
		DE-D-	69203623	31-08-95
		DE-T-	69203623	11-01-96
		ES-T-	2074835	16-09-95
		JP-A-	4327563	17-11-92
FR-A-2614787	10-11-88	JP-A-	63275506	14-11-88
EP-A-0406162	02-01-91	CH-A-	677886	15-07-91
		CA-A-	2019710	26-12-90
		DE-D-	59002618	14-10-93
		JP-A-	3047527	28-02-91
		US-A-	5152923	06-10-92
EP-A-0257454	02-03-88	JP-A-	63048214	29-02-88
WO-A-9315736	19-08-93	AU-B-	3721593	03-09-93
		CA-A-	2130357	19-08-93
		EP-A-	0626850	07-12-94
		US-A-	5472706	05-12-95
		ZA-A-	9301143	14-09-93
US-A-5368857	29-11-94	AU-B-	8140894	06-06-95
		CA-A-	2169079	26-05-95
		WO-A-	9513791	26-05-95
WO-A-9410131	11-05-94	AU-B-	5373894	24-05-94
		EP-A-	0667853	23-08-95
		JP-T-	8502961	02-04-96
		ZA-A-	9308141	02-05-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 96/00493

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9320038	14-10-93	AU-B-	4959093	08-11-93
		CA-A-	2131184	14-10-93
		EP-A-	0633875	18-01-95
WO-A-9423694	27-10-94	AU-B-	6677494	08-11-94
		CA-A-	2159201	27-10-94
		EP-A-	0695167	07-02-96
		ZA-A-	9402678	19-10-95